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EXAMINER

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 09/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/756,978

Applicant(s)

ROUSSEL, EUGENE

Examiner

Karen A Canella

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-66,81 and 83 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-61,81 and 83 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: ____.

DETAILED ACTION

1. Please note that the examiner assigned to this application has changed.
2. After review and reconsideration, the finality of the Office action mailed November 25, 2003 is withdrawn.
3. Claims 1-66, 81 and 83 are pending and under consideration.
4. Text of Title 35, US Code not found in this action can be found in a previous action.
5. Claim 24 is objected to because of the following informalities: "eotaxin" appears to be spelled as "cotaxin". Appropriate correction is required.
6. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
7. Claims 1-66, 81 and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
 - (A) Claims 1, 66, 81 and 83 recite "a second type 1 inflammatory response promoting agent" without reciting the "first type 1 inflammatory response promoting agent".
 - (B) The term "strong" in claim 3 is a relative term which renders the claim indefinite. The term "strong" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.
 - (C) Claim 22 is vague and indefinite in the recitation of "granular component P2". The exact term "granular component P2" is unknown in the art and it is not clear if applicant is claiming a method dependent on the use of polypreforin P2" (Berke and Rosen, Transplantation

Proceedings, 1987, Vol. XIX, pp. 412-416), or if applicant is intending to claim a method using a different protein.

(D) It is unclear how claim 37 further limits claim 1. Claim 1 recites iia) locally administering to the tumor a leukocyte attractant whereby leukocytes are induced to infiltrate the tumor. Claim 37 recites iii) locally administering to the tumor a type 1 lymphocyte attractant in order to sustain the type 1 inflammatory response. It is unclear if the type 1 lymphocyte attractant represents a second dose of the type 1 lymphocyte attractant apart from the dose administered in section iia), or if the administration of the type 1 lymphocyte attractant of claim 37 further describes the dose used to elicit the infiltrating leukocytes of section iia). For purpose of examination, both alternatives will be considered.

(E) Claim 38 is vague and indefinite because it is unclear which "type-1 lymphocyte attractant" is being referenced, because claim 38 is dependent on claim 37 which is dependent on claim 1: claim 1 recites type 1 lymphocyte attractant in section iib and claim 37 also incorporates in section iii a type 1 leukocyte attractant. Therefore it is unclear if the lymphocyte attractant of claim 38 is referring to the section ii b or the section iii lymphocyte attractant or both.

(F) Claim 39 is vague and indefinite because it is unclear if both of the IP-10 and Mig must be administered together as the leukocyte attractant or if IP-10 or Mig is the leukocyte attractant.

(G) Claims 46, 47 and 48 are vague and indefinite in the recitation of "an independently selected IR1-promoting agent". It is unclear how the IR1-promoting agent is "independent selected" and it is unclear how the "selected" IR1 promoting agent differ from a IR1 promoting agent.

8. Claim 56 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 56 embodies the method of claim 53 wherein the memory cell inducing agent is administered after the tumor shrinks to less than 10 percent of its size immediately prior to administration of the antigen-releasing agent. Claim 52 is dependent on claim 1 which is drawn

to a method of inducing tumor cell death in a human patient comprising (i) administering an antigen releasing agent to the tumor. The specification describes the use of antigen-releasing agents as a first step in the claimed method. Claim 56 requires that the tumor shrinks to less than 10 percent of its size immediately prior to the administration of the antigen-releasing agent. The state of the art with regard to cancer therapy is highly complex and unreliable. The claim requires a tumor shrinkage to less than 10 percent of its original size before the administration of the antigen-releasing agent of the claimed method. The specification provides not guidance for how to shrink said tumor beyond the instant method which would require the administration of the antigen-releasing agent. Given the lack of teachings in the specification for alternative methods of shrinking the tumor that do not require implementation of the claimed invention, one of skill in the art would be subject to undue experimentation in order to shrink the tumor to the required size before the administration of the antigen-releasing agent of the claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claim 83 is rejected under 35 U.S.C. 102(e) as being anticipated by Yu (U.S. 2002/0044919, priority to 60/177,024) as evidenced by the abstract of Curtiss (Arteriosclerosis and Thrombosis, 1994, Vol. 14, pp. 47-53).

Claim 83 is drawn to a method of inducing a tumor cell death in a human patient, the method comprising locally co-administering to a solid tumor in the patient an antigen-releasing

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agent, a leukocyte attractant, interferon gamma and a second type 1 inflammatory response promoting agent.

Yu discloses a method for treating neoplasms in mammal comprising inducing the coagulation of a tumor in a mammal by protein denaturation, oxidation, reduction and physical methods such as cryotherapy, laser coagulation, radiation, percutaneous microwave coagulation, radio-frequency induced coagulation, ultrasonic coagulation, transpupillary thermotherapy and electrochemotherapy (Figure 1). Yu discloses that these agents and method induce an inflammatory response to the resulting coagulated tissue mass (page 1, paragraph 0009, lines 1-4). Yu discloses three-in-one intratumoral injection therapy to induce coagulation (page 1, paragraph 0009, lines 4-11). Yu discloses that the area of inflammation attracts lymphocytes and other inflammatory response mediators to the target tumor site and that these lymphocytes are exposed to tumor antigens via the process of coagulation and killing of the tumor cells, wherein said exposure of lymphocytes elicits a tumor-specific immune response (page 2, paragraph 0019). Yu discloses a three in one combination for intratumoral injection (figure 2), wherein said combination includes an oxidizing agent or a reducing agent, a protein denaturation agent or other coagulating means or treatment and a hapten (page 1, paragraph 0009). Yu discloses that immunologic adjuvants, such as interferons can also be administered with the three in one combination (page 2, paragraph 0018). Yu discloses that antiangiogenic agents can be administered with the combination, and specifically discloses interferon-gamma, IL-1, IL-2 as preferred embodiments (page 2, paragraph, 0022 and page 3, paragraph 0024, line 21), thus fulfilling the specific embodiments of sections iii and iv. Yu discloses that the combination may comprise the gene encoding IL-8 (page 16, paragraph 0148, lines 12-16). The abstract of Curtiss provides evidence that IL-8 is a potent chemoattractant for T-lymphocytes, thus fulfilling the specific embodiment of section (ii), specifying a leukocyte attractant.

It is noted that Yu specifically discloses the administration of a hapten as part of the three in one combination. The instant claims are drawn to a method "comprising" therefore the method as claimed does not exclude the administration of a hapten.

11. Claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu (US 2002/0044919, priority to 60/177,024, filed

January 19, 2000) in view of Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536).

Claim 1 is drawn to a method of inducing tumor cell death in a human patient, the method comprising locally administering an antigen-releasing agent to a solid tumor in the patient whereby a tumor antigen is released from cells in the tumor; locally administering to the tumor a leukocyte chemoattractant, whereby leukocytes are induced to infiltrate the tumor; and, locally administering to the tumor IFN-gamma and a second type 1 inflammatory response promoting agent, whereby a type 1 inflammatory response is induced in the tumor and tumor cell death is induced. Claim 2 embodies the method of claim 1 wherein the antigen releasing agent is a tumor debulking agent. Claim 3 embodies the method of claim 1 wherein the antigen-releasing agent comprises an agent selected from the group consisting of a proteolytic enzyme, an apoptosis-inducing agent, electrical current, strong acid and a strong base. Claim 5 embodies the method of claim 3 wherein the antigen-releasing agent comprises one proteolytic enzyme. Claim 10 embodies the method of claim 3 wherein the antigen-releasing agent is electrical current delivered by way of electrodes inserted into the tumor. Claim 14 embodies the method of claim 1 wherein the antigen-releasing agent and the leukocyte attractant are co-administered to the tumor. Claim 16 embodies the method of claim 1 wherein the antigen-releasing agent and the IFN-gamma are co-administered into the tumor. Claim 17 embodies the method of claim 1 wherein the leukocyte attractant comprises a monocyte attractant. Claim 18 embodies the method of claim 17 wherein the monocyte chemoattractant is selected from the group consisting of MCP-1, -2, -3 and -4. Claim 19 embodies the method of claim 1 wherein the leukocyte attractant comprises a T-cell attractant. Claim 20 embodies the method of claim 19 wherein the T-cell attractant is RANTES, IP-10 or Mig. Claim 25 embodies the method of claim 1 wherein the leukocyte attractant is co-administered with at least one of IFN-gamma and the second IR-1 promoting agent. Claim 28 embodies the method of claim 1 wherein the leukocyte attractant and at least one of IFN-gamma and the second Ir-1 promoting agent are co-administered. Claim 29 embodies the method of claim 1 wherein the second IR-1 promoting agent is selected from the group consisting of Il-2, Il-12, TNF-alpha and TGF-b. Claim 30 embodies the method of claim 29 wherein the second IR-1 promoting agent comprises Il-2. Claim 34 embodies the method of

claim1 wherein IFN-g and the second IR-1 promoting agent are co-administered. Claim 52 embodies the method of claim 1 further comprising administering memory-cell inducing agent to the patient after inducing the type 1 inflammatory response, whereby production of anti-tumor type 1 immune memory cells is enhanced.

Claim 37 embodies the method of claim 1 further comprising locally administering to the tumor a type 1 lymphocyte attractant in order to sustain the type 1 inflammatory response. Claim 38 embodies the method of claim 37 wherein the type-1 lymphocyte attractant is selected from the group consisting of RANTES, IP-10 and Mig. Claim 39 embodies the method of claim 37 wherein the type-1 lymphocyte attractant comprises IP-10 and Mig. Claim 40 embodies the method of claim 37 further comprising sustaining the type-1 inflammatory response by locally administering autologous leukocytes to the tumor. Claim 41 embodies the method of claim 37 further comprising administering a memory-cell inducing agent to the patient after inducing the type 1 inflammatory response, whereby production of anti-tumor type 1 immune memory cells is enhanced.

Claim 44 embodies the method of claim 1 further comprising locally administering autologous leukocytes to the tumor. Claim 45 embodies the method of claim 44 wherein the autologous leukocytes are obtained from a patient and expanded prior to the local administration. Claim 46 embodies the method of claim 44 wherein the autologous leukocytes are obtained from the patient and contacted with a IR-1 promoting agent prior to the local administration. Claim 47 embodies the method of claim 44 wherein the autologous leukocytes are obtained from the patient, expanded in vivo, and contacted with an IR-1 promoting agent prior to the local administration. Claim 48 embodies the method of claim 47 wherein the leukocytes are contacted with the IR-1 promoting agent and with at least one of IFN-a and Il-12 prior to the local administration. Claim 49 embodies the method of claim 44 wherein the method further comprises administering a memory-cell inducing agent to the patient after inducing the type-1 inflammatory response, whereby production of anti-tumor type1 immune memory cells is enhanced.

Claim 81 is drawn to a method of inducing a type 1 inflammatory response at the site of a solid tumor in a human patient, the method comprising locally administering an antigen-releasing agent to the tumor; locally administering to the tumor a leukocyte attractant; and

locally administering to the tumor INF-gamma and a second type1 inflammatory response promoting agent.

Yu teaches a method for killing tumor cells in a mammal, said method comprising inducing the coagulation of a tumor in a mammal by protein denaturation, oxidation, reduction and physical methods such as cryotherapy, laser coagulation, radiation, percutaneous microwave coagulation, radio-frequency induced coagulation, ultrasonic coagulation, transpupillary thermotherapy and electrochemotherapy (Figure 1). It is noted that the disclosure of “electrochemotherapy” fulfills the specific embodiment of claim 10, specifying the delivery of electrical current to the tumor. Yu teaches that these agent and methods induce an inflammatory response to the resulting coagulated tumor tissue (page 1, paragraph 0009, lines 1-4). Yu teaches that the area of inflammation attracts lymphocytes and other inflammatory response mediators to the target tumor site, and that said lymphocytes are exposed to tumor antigens released by the coagulated cells as the target tumor site, thus eliciting tumor specific immune responses (page 2, paragraph 0019). Yu specifically teaches a “three in one” combination for intratumoral injection to induce coagulation, wherein said combination includes an oxidizing or reducing agent, a protein denaturation agent or a physical means of coagulation, and a hapten (page 1, paragraph 0009). Yu teaches that a protein denaturation agent can be a cellular lysing agent such as proteinase K or pancreatin (page 18, paragraph 0167), thus fulfilling the specific embodiment of claims 3 and 5 specifying a proteolytic enzyme. Yu teaches that protein denaturation can also be attained by chemical treatment to reach acidic conditions of pH from about 2 to about 5; Yu specifically teaches sodium citrate as a specific embodiment of a protein denaturation agent (page 18, paragraph 0172, line 3 and lines 13-15), thus fulfilling the specific embodiments of claim 3 specifying a strong acid. Yu teaches that other agents an be included in the combination and specifically teaches INF-gamma, Il-1 and Il-2 as preferred embodiments (page 2, paragraph 0022 and page 3, paragraph 0024, line 21) , thus fulfilling the specific embodiments of claim 81, section iib because Il-2 is the “second” type 1 inflammatory response promoting agent as defined by the instant disclosure. Yu teaches that anti-angiogenic agents may be administered in the three-in-one combination as specifically recites Il-12 (page 3, paragraph 0024, line 21) as well as angiostatic chemokines such as IP-10, Mig and SDF-1alpha (page 18, paragraph 0174, lines 43-47). The administration of Ip-10 and Mig satisfy the specific embodiments of claims 19 and 20.

Yu does not specifically teach the induction of a type 1 inflammatory response, or the inclusion of a chemokine for purpose of attracting leukocytes, although Yu teaches that the coagulum itself attracts lymphocytes.

Nishimura et al teach that Th1 cells eradicated the tumor through cell-mediated immunity, but that Th2 cells eradicated the tumor mass by necrosis. Nishimura et al demonstrate that the therapeutic effect of both Th1 and Th2 cells was achieved by cooperation with CD+8 T-cells in the tumor bearing host (page 854, first column, lines 9-16). Nishimura et al teach that in mice cured of tumors by Th2 therapy, do not acquire immunological memory but that mice cured of tumors by Th1 therapy produce memory cytotoxic T-lymphocytes (page S58, second column, lines 1-5). Nishimura et al teach that Th1 cells produce high levels of IFN-g, and the chemokines RANTES, MIP-1alpha and beta (page S53, Table 1). The administration of RANTES would satisfy the specific embodiment of claims 19 and 20. Nishimura et al also teach that Th2 cells produce high levels of Il-6 and Il-10 which cause cachexia in tumor bearing hosts and that considering only Th1 therapy was able to induce memory CTL, conclude that Th-1 dominant immunity is superior to Th2 immunity for application in tumor immunotherapy (page S58, second column, lines 14-19). Nishimura et al teach that tumor specific Th1 cells could be induced from tumor-infiltrating lymphocytes by culture with Il-2 and Il-12 and suggest that said resulting Th1 cells would be applicable to adoptive immunotherapy in both animal and human systems (page S54, second column, lines 4-10), thus fulfilling the specific embodiment of claims 44-48 as drawn to TIL cultured in the presence of Il-12.

Cameron et al teach that the administration of tumor infiltrating lymphocytes, Il-2 and local tumor irradiation results in synergistic anti-tumor activity. It is noted that "radiation" is taught by Yu as a means to induce tumor coagulation (above) and thus provide a source of tumor antigen. Cameron et al provide evidence against the notion that the radiation-induced augmentation of TIL anti-tumor activity was the elimination of suppressor cells (page 261, under the heading "Summary", line 26 to page 262, line 5). Cameron et al teach that the TIL were obtained from tumors and expanded ex vivo in the presence of Il-2 (page 250, under the heading "TIL").

Ferrero et al teach that murine and human tumors release tumor-derived chemotactic factors which regulate the recruitment of tumor-associated macrophages and leukocytes (page

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2530, second column, lines 6-9), thus corroborating the teachings of Yu regarding the attraction of lymphocytes to the coagulum. Ferrero et al teach that in renal cancer both MCP-1 and Il-8 are secreted by the tumor cells (page 2531, first column, lines 8-14). Ferrero et al teach that the addition of recombinant MCP-1 or Il-8 in the absence of tumor cells can cause an increase in TIL matrix invasion (page 2531, first column, line 17 to second column, line 5). The administration of MCP-1 or Il-8 would satisfy the specific embodiments of claims 17-19 because Il-8 is a T-cell chemokine as taught by Ferraro et al (abstract, lines 3-5).

It would have been prima facie obvious to induce a Th1 specific immune response in the presence of a tumor coagulum using the method taught by Yu. It would have been further obvious to administer TIL which were cultivated ex vivo with Il2 and Il12 and administer said TIL in addition to a chemokine, such as MCP-1 or SDF-1alpha, and/or to administer Il-12 as a memory cell inducing agent. One of skill in the art would have been motivated to do so by the teachings of Nishimura et al on the generation of tumor specific Th1 cells from tumor-infiltrating lymphocytes by culture with Il-2 and Il-12 and suggestion by Nishimura et al that said resulting Th1 cells would be applicable to adoptive immunotherapy in both animal and human systems. One of skill in the art would be further motivated to induce a Th1 response rather than exclusively a Th2 response in order to avoid the side-effects associated with cytokines of the Th2 response and to attain memory CTL, which, as taught by Nishimura et al, were only produced by Th1 treatment. One of skill in the art would reasonably conclude from the teachings of Nishimura et al that the production of high levels of IFN-g, and the chemokines RANTES, MIP-1alpha and beta by Th1 cells is necessary for the induction of memory CTL, and thus one of skill in the art would be motivated to administer IFN-g and the Th1 chemokines in addition to Il-12 in order to assure the maintenance of the Th1 immune response state and the induction of memory CTL. One of skill in the art would be motivated to combine the teachings of Nishimura et al with the teachings of Yu because of the teachings of Cameron et al on the synergist effect of a tumor coagulation treatment, local tumor irradiation, and administered TIL. One would reasonably conclude when viewing Cameron et al in light of Yu, that the local tumor irradiation was acting to kill tumor cells, producing a local coagulum and local concentration of tumor antigens which are released from necrotic cells. One of skill in the art would be motivated to take advantage of the tumor antigens released by the irradiation and administer an

immunotherapeutic in the form of TIL which are demonstrated by Cameron et al to synergize with the local tumor irradiation. One of skill in the art would be motivated to locally administer a chemokine in combination with the intratumoral injection taught by Yu to further recruit inflammatory cells to the tumor coagulum in order to take advantage of the abundance of tumor antigens released from the necrotic tumor cells within said coagulum, and because Yu teaches that the chemokines of IP-10, Mig and SDF-1alpha have anti-angiogenic effects which are desirable in the killing of tumor cells. One of skill in the art would also be motivated to enhance and sustain the Th1 inflammatory response by further administering TIL, inflammatory response type 1 cytokines and chemokines in order to more fully kill the tumor cells and induce a wide range of anti-tumor memory CTL.

12. Claims 1-3, 5, 7-10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) as applied to claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, in further view of Rovere et al (Journal of Immunology, 1998, Vol. 161, pp. 4467-4471) and Mollinedo et al (Cancer Research, 1997, Vol. 57, pp. 1320-1328) and Boggs et al (Biochimica et Biophysica Acta, 1998, Vol. 1389, pp. 1-12).

Claim 7 embodies the method of claim 3 wherein the antigen-releasing agent comprises an alkylphospholipid. Claim 8 embodies the method of claim 7 wherein the alkylphospholipid is an alkylphosphocholine. Claim 9 embodies the method of claim 7 wherein the alkylphosphocholine is hexadecylphosphocholine and edelfosine.

The combination of Yu and Nishimura et al and Cameron et al and Ferrero et al render obvious the specific embodiments of claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37, 41, 44-49 and 81 for the reasons set forth above. It is noted that Yu teaches the administration of genes encoding apoptotic proteins as part of the method (page 19, paragraph 0177, lines 12-13). Yu teaches dendritic cells as part of the lymphocytes which are attracted to the tumor coagulum, and the exposure of said dendritic cells to tumor antigens generated from the tumor cell lysis and the elicitation of a tumor specific immune response thereby (page 2, paragraph 0019, lines 9-13). It

is also noted that Nishimura et al also teach the generation of dendritic cells under Th1 conditions which include GM-CSF, IL-3, IL-12, and IFN-g (page S56, second column, lines 1-6, under the heading "Induction of Th-1 dominant immunity by dendritic cell based vaccination"). Nishimura et al teach that once the dendritic cells were conditioned by Th1 cytokine, they could replace helper T-cell function and support the generation of CTLs from naïve CD+8 T-cells in the absence of helper T-cells (page S56, second column, lines 24-30). None of the aforesaid references teach the administration of an apoptosis agent as an antigen-releasing agent nor the specific apoptosis inducing agents of hexadecylphosphocholine and edelfosine.

Rovere et al teach that high numbers of apoptotic cells mimic a failure of normal in vivo clearance are sufficient to trigger dendritic cell maturation and the presentation of antigens from apoptotic cells (abstract, lines 9-13).

Mollinedo et al teach Edelfosine as a phosphocholine which selectively induces apoptosis in cancer cells including human leukemia cells and in primary tumor cell cultures (abstract), including human colon carcinoma (page 1321, first column, lines 14-16). Boggs et al teach that hexadecylphosphocholine led to the accumulation of cells in G2/M phase, triggered DNA fragmentation and caused morphological changes associated with apoptosis (abstract).

It would have been prima facie obvious at the time the claimed invention was made to locally administer hexadecylphosphocholine or edelfosine to the tumor in order to induce a high level of apoptotic tumor cells which would be taken up by the Th1 primed dendritic cells attracted to the tumor coagulum by virtue of the administered Th1 cytokines and chemokines, and cross presented to naïve CD+8 T cells to attain tumor specific CTL. One of skill in the art would have been motivated to do so by the teachings of Rovere et al who indicate that dendritic cells can take up apoptotic cells and present them when the level of apoptotic cells are quite high, and the teachings of Nishimura et al on the ability of dendritic cells, primed with Th1 cytokines, to activate naïve CD+8 T-cells and support CD+8 T-cells in the absence of T-helper cells. One of skill in the art would be motivated to administer the known apoptotic agents of hexadecylphosphocholine or edelfosine because said agents have specificity toward tumor cells and it is reasonably concluded that said agents will not induce apoptosis in the dendritic cells or T-cells.

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13. Claims 1-3, 5, 10, 14, 16-22, 25, 28-30, 34, 37-41, 44-49, 52 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) as applied to claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, in further view of Sager et al (WO 92/01039).

Claim 21 embodies the method of claim 1 wherein the leukocyte attractant is selected from the group consisting of Il-8, granular component P-2, growth related oncogen-1, -2, -3, neutrophil activated protein and neurotatin.

The combination of Yu and Nishimura et al and Cameron et al and Ferrero et al render obvious the specific embodiments of claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37, 41, 44-49 and 81 for the reasons set forth above. It is noted that Yu teaches the administration of a gene encoding Il-8 to enhance the immune response against the tumor coagulum (page 19, paragraph 0177, lines 13-18). None of the aforesaid references specifically teach the administration of a leukocyte attractant which is a granulocyte attractant, although Nishimura et al teach that the Th1 conditions for dendritic cells include GM-CSF.

Sager et al teach the GRO proteins (Growth Related Oncogen proteins) which are maturation factors and chemo-attractants for granulocytes (page 22, lines 10-21, claims 1 and 13). Sager et al also teach the local administration of GRO directly to the site to be treated (page 23, lines 30-31).

It would have been prima facie obvious at the time the claimed invention was made to administer the growth related oncogen protein of Sager et al as part of the method of killing tumor cells rendered obvious by Yu and Nishimura et al and Cameron et al and Ferrero et al. One of skill in the art would be motivated to do so in order to increase the number of PMNs recruited to the tumor coagulum. One of skill in the art would be motivated to involve as many types of immune cells as possible in order to take advantage of the increased level of tumor antigen released by the tumor coagulum and kill the greatest number of tumor cells.

14. Claims 1-3, 5, 10, 14, 16-21, 23-25, 28-30, 34, 37-41, 44-49, 52 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al

(Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) as applied to claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, in further view of Garcia-Zepeda et al (Nature Medicine, 1996, Vol. 2, pp. 449-456).

Claim 23 embodies the method of claim 21 wherein the granulocyte attractant is a eosinophil attractant. Claim 24 embodies the method of claim 23 wherein the eosinophil attractant is eotaxin.

The combination of Yu and Nishimura et al and Cameron et al and Ferrero et al render obvious the specific embodiments of claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37, 41, 44-49 and 81 for the reasons set forth above. It is noted that Yu teaches the administration of a gene encoding Il-8 to enhance the immune response against the tumor coagulum (page 19, paragraph 0177, lines 13-18). None of the aforesaid references specifically teach the administration of a leukocyte attractant which is a granulocyte attractant, although Nishimura et al teach that the Th1 conditions for dendritic cells include GM-CSF.

Garcia-Zepeda et al teach that human eotaxin is a specific chemoattractant for eosinophils. Garcia-Zepeda et al teach that upon activation, eosinophils release preformed toxic cationic granule proteins, such as major basic protein, eosinophilic cationic protein and eosinophil peroxidase, and that eosinophils generate oxidative products, hyphalous acids, lipid mediators and cytokines that contribute to the eosinophils pro-inflammatory function (page 449, column 1, lines 5-13). Garcia-Zepeda et al teach that human eotaxin is induced by pro-inflammatory cytokines of TNF-a, Il-1a and IFN-g in both endothelial and epithelial cells which then recruit eosinophils from the blood into the tissue (page 454, first column, lines 27-33). Garcia-Zepeda et al teach that if a Th1 response predominates, eosinophils are recruited and contribute to tissue damage (page 454, first column, lines 61-63).

It would have been prima face obvious at the time the claimed invention was made to administer eotaxin in the method rendered obvious by the combination of Yu and Nishimura et al and Cameron et al and Ferrero et al. One of skill in the art would be motivated to do so in order to increase the tissue damage inflicted by the inflammatory cells on the remaining tumor cells.

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15. Claims 1-3, 5, 10, 12, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) as applied to claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, in further view of Wang et al (Molecular and Cellular Biology, 1995, Vol. 15, pp. 1759-1768) and Ausubel et al (Short Protocols in Molecular Biology, second edition, 1992 page 1-20).

Claim 12 embodies the method of claim 3 wherein the antigen-releasing agent comprises a strong base selected from the group consisting of sodium hydroxide and potassium hydroxide.

Neither of the aforesaid references specifically teach strong base as an antigen releasing agent although Yu teach tumor coagulation, which is the same as tumor cell lysis, by chemical methods which include oxidative chemicals and chemicals which are reducing agents (Figure 1).

It is well known in the art, that alkaline lysis is a method to lyse bacterial cells as exemplified by Ausubel et al (page 1-20). Wang et al teach alkaline lysis as a method of lysing mammalian cells (page 1761, first column, lines 4-5 under the heading of "Shuttle vector isolation and analysis"). It would have been prima facie obvious at the time the claimed invention was made to use sodium or potassium hydroxide as a means for producing the tumor coagulum in the method of Yu. One of skill in the art would be motivated to use a hydroxide base as a method of inducing tumor coagulation because it is well recognized in the art that sodium hydroxide, which is a strong base, can lyse bacterial cell walls as well as the cell membranes of mammalian cells.

16. Claims 1-3, 5, 10, 11, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) as applied to claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, in further view of Cerami et al (EPO 310,136) and the abstract of DeSanctis et al (Seminars in Interventional Radiology, 1997, Vol. 14, pp. 255-284)..

Claim 11 embodies the method of claim 3 wherein the antigen-releasing agent comprises a strong acid selected from the group consisting of hydrochloric acid and sulfuric acid.

Neither of the aforesaid references specifically teach strong acid as an antigen releasing agent although Yu teach tumor coagulation, which is the same as tumor cell lysis, by chemical methods which include chemical treatment to reach acidic conditions of pH from about 2 to pH of about 5 (page 18, paragraph 0172, lines 13-15).

Cerami et al teach a method for lysing mammalian cells comprising cell lysis with .4N hydrochloric acid in isopropanol (page 13, line 30).

The abstract of DeSanctis et al teaches ablation of liver tumors using percutaneous injection of acetic acid

It would have been prima facie obvious at the time the claimed invention was made to use hydrochloric acid in isopropanol as a means for producing the tumor coagulum in the method of Yu. One of skill in the art would have been motivated to do so by the teachings of the abstract of DeSanctis et al who demonstrates tumor ablation by the percutaneous injection of acetic acid and the specific teachings of Cerami et al on cellular lysis induced by .4 N hydrochloric acid in isopropanol.

17. Claims 1-5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) as applied to claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, in further view of Semple et al (US 6,011,047).

Claim 4 embodies the method of claim 3 wherein the antigen-releasing agent comprises a proteolytic enzyme selected from the group consisting of trypsin, chymotrypsin, pepsin and collagenase.

The combination of Yu and Nishimura et al and Cameron et al and Ferrero et al render obvious the specific embodiments of claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37, 41, 44-49 and 81 for the reasons set forth above. Neither of the aforesaid references teach the administration of trypsin, chymotrypsin, pepsin or collagenase as a means to cause lysis of tumor

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cells, although Yu teaches proteolytic enzymes such as proteinase K or pancreatin (page 4, paragraph 0037).

Semple et al teach that elevated levels of trypsin and chymotrypsin within pancreatic acinar cells cause auto-digestion and coagulation necrosis within the pancreas and surrounding tissues (column 36, lines 30-38).

It would have been prima facie obvious at the time the claimed invention was made to use trypsin or chymotrypsin to induce coagulation necrosis in the method as taught by Yu. One of skill in the art would have been motivated to do so by the teachings of Yu on the use of pancreatin in the method of inducing tumor necrosis and the teachings of Semple et al on the induction of coagulation necrosis by elevated levels of trypsin and chymotrypsin.

18. Claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-52, 57-66 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) and Rovere et al (Journal of Immunology, 1998, Vol. 161, pp. 4467-4471) and Mollinedo et al (Cancer Research, 1997, Vol. 57, pp. 1320-1328) and Boggs et al (Biochimica et Biophysica Acta, 1998, Vol. 1389, pp. 1-12) as applied to claims 1-3, 5, 7-10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, and further in view of the abstract of Aker (Cancer, 1979, Vol. 43, suppl., pp. 2103-2107) and the abstract of Johnston (Journal of Human Nutrition, 1979, Vol. 33, pp. 189-196).

Claims 42, 43, 50, 51 and 57 embody the methods of claims 41, 37, 49, 44 and 1, respectively, further comprising providing a vitamin and a mineral to supplement the patients nutrition. Claim 58 embodies the method of claim 57 when the vitamin is selected from the group consisting of A, B, C, D and E, Claim 59 embodies the method of claim 58 wherein the vitamin is C and wherein the patient receives 200 to 400 milligrams of vitamin C daily. Claim 60 embodies the method of claim 58, wherein the vitamin is E, and the patient receives from 200 to 400 IU of vitamin E daily. Claim 61 embodies the method of claim 57 wherein the mineral is selected from the group consisting of selenium, zinc, calcium, magnesium, iron and copper. Claim 62 embodies the method of claim 61 wherein the mineral is selenium and wherein the

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patient receives from 200 to 400 mg of selenium daily. Claim 63 embodies the method of claim 61 wherein the mineral is zinc and the patient receives from 15 to 100 mg of zinc daily. Claim 64 embodies the method of claim 57 wherein the patient is supplemented beginning at least on the same day that the antigen-releasing agent is administered to the tumor and continuing at least until the same day that IFN-g is administered. Claim 65 embodies the method of claim 57 wherein the patient's nutrition is supplemented beginning at least five days before the antigen releasing agent is administered to the tumor and continuing through at least three days after the day IFN-g is administered.

Claim 66 is drawn to a method of inducing tumor cell death in a human patient comprising supplementing the patients nutrition with a nutrient selected from a vitamin and a mineral; locally administering an antigen-releasing agent; locally administering a leukocyte attractant whereby leukocytes are induced to infiltrate the tumor; locally administering IFH-g and a second type 1 inflammatory response promoting agent, whereby a type 1 inflammatory response is generated in the tumor; and sustaining the type 1 inflammatory response by locally administering t type 1 lymphocyte attractant, and/or locally administering autologous leukocytes to the tumor.

Neither of the aforesaid references teach the supplementation of a patients nutrition either before or during treatment.

The abstract of Aker teaches that it is important to maintain a cancer patient's nutritional status, and that nutritional supplements must be chosen to meet the individual patient's needs. The abstract of Johnston teaches that the nutritional state of patients with malignant disease must be assed at the beginning of treatment and that nutritional supplements can be given to enable patients to better tolerate the treatment, and that clinical response may be enhanced by nutritional support.

It would have been prima facie obvious at the time the claimed invention was made to administer both vitamins and mineral to patients before the treatment commences or at the time the treatment commences. One of skill in the art would have been motivated to do so by the teachings of the abstracts of Aker and Johnston who stress the importance of the nutritional requirements of cancer patients and the suggestion in the abstract of Johnston that clinical response might be enhanced by nutritional support.

19. Claims 1-3, 5, 10, 14, 16-20, 25, 28-33, 34, 37-41, 44-49, 52 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) as applied to claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, in further view of Bottomly et al (US 2002/0090381, priority to April 9, 1999).

Claim 31 embodies the method of claim 29, wherein the second IR-1 promoting agent comprises TNF-b. Claim 32 embodies the method of claim 29 wherein the second IR-1 promoting agent comprises both IL-2 and TNF-b.

The combination of Yu and Nishimura et al and Cameron et al and Ferrero et al render obvious the specific embodiments of claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37, 41, 44-49 and 81 for the reasons set forth above. Neither of the aforesaid references teach the administration of TNF-b as a IR-1 promoting agent.

Bottomly et al teach a method of modulating an immune response comprising the administration of cytokines which bias the individual's immune response from a Th1 or Th2 response (page 2, paragraph 0016). Bottomly et al teach that TNF-b is a Th1 cytokine (page 3, paragraph 0027, lines 13-15).

It would have been prima facie obvious at the time the claimed invention was made to include TNF-b as an additional modulator of the TH1 immune response. One of skill in the art would have been motivated to do so by the teachings of Bottomly et al on the role of TNF-b as a Th1 cytokine.

20. Claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52-54 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) as applied to claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, in further view of Grooten et al (WO 98/36768).

Claim 53 embodies the method of claim 52 wherein the memory cell inducing agent is selected from the group consisting of Il-15 and IFN-a. Claim 54 embodies the method of claim 52 wherein the memory cell inducing agent is Il-15.

The combination of Yu and Nishimura et al and Cameron et al and Ferrero et al render obvious the specific embodiments of claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37, 41, 44-49 and 81 for the reasons set forth above. Neither of the aforesaid references teach the administration of Il-15 as a memory cell inducing agent, although the combination renders obvious the use of Il-12 as a memory cell inducing agent.

Grotten et al teach that the administration of Il-15 during or after a primary immune response results in an augmented proliferative response of cells from draining lymph nodes against antigen which is indicative of memory T-cells in the immunized animal (pages 1-2, bridging sentence, page 18, lines 11-14 and pages 20-21, bridging paragraph).

It would have been prima facie obvious at the time the claimed invention was made to administer Il-15 as a memory cell inducing agent. One of skill in the art would have been motivated to do so by the teachings of Nishimura et al on the desirability of inducing memory T-cells to a tumor associated antigen and the teachings of Grotten et al that identify Il-15 as a memory T-cell inducing agent.

21. Claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52, 53, 55 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) as applied to claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, in further view of Tuting et al (Journal of Immunology, 1998, Vol. 160, pp. 1139-1147).

Claim 55 embodies the method of claim 52 wherein the memory cell inducing agent is IFN-a.

The combination of Yu and Nishimura et al and Cameron et al and Ferrero et al render obvious the specific embodiments of claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37, 41, 44-49 and 81 for the reasons set forth above. Neither of the aforesaid references teach the

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administration of Il-15 as a memory cell inducing agent, although the combination renders obvious the use of Il-12 as a memory cell inducing agent.

Tuting et al teach that dendritic cells transfected with genes encoding Il-12 and IFN- α elicit primary cytotoxic T-cell responses in vitro (abstract).

It would have been prima facie obvious at the time the invention was made to administer IFN- α as an additional Th1 promoting agent. One of skill in the art would have been motivated to do so by the teachings of Nishimura et al on the production of memory T-cells in mice treated with Th1 therapy (page S58, second column, lines 1-5) and the teachings of Tuting et al identifying IFN- α as a Th1 biasing cytokine.

22. Claims 1-3, 5, 6, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) as applied to claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, in further view of what is recognized in the art

Claim 6 embodies the method of claim 3 wherein the antigen-releasing agent comprises at least two proteolytic enzymes.

It would have been prima facie obvious to use at least two proteolytic enzymes in the method of inducing tumor coagulation as taught by Yu.

The instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been taught individually in the prior art. Applying the same logic to the instant process claims, given the teaching of the prior art of methods of using a composition comprising a single proteolytic enzyme such as proteinase K or pancreatin as taught by Yu in compositions for the treatment of cancer, it would have been obvious to use more than one proteolytic enzyme collectively for the treatment of tumors

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because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as agents for inducing tumor coagulation.

One of skill in the art would have been motivated to do so because each of proteinase K and pancreatin were taught by Yu to be useful in inducing tumor coagulation.

23. Claims 1-3, 5, 6, 10, 13-20, 25-30, 33-41, 44-49, 52, 56 and 81 are rejected over Yu (US 2002/0044919, priority to 60/177,024, filed January 19, 2000) and Nishimura et al (Cancer Chemother Pharmacol, 2000, Vol. 46 (suppl.), pp. S52-S61) and Cameron et al (Journal of Experimental Medicine, 1990, Vol. 171, pp. 249-263) and Ferrero et al (European Journal of Immunology, 1998, Vol. 28, pp. 2530-2536) as applied to claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37-41, 44-49, 52 and 81 above, in further view of what is recognized in the art

Claim 13 embodies the method of claim 1 wherein the antigen-releasing agent is administered to the tumor at least two hours before administering the leukocyte attractant. Claim 15 embodies the method of claim 1, wherein the antigen-releasing agent is administered to the tumor at least two hours before administering IFN-g. Claim 26 embodies the method of claim 1 wherein the leukocyte attractant and the at least one of IFN-g and the second IR-1 promoting agent are administered not more than two hours apart. Claim 33 embodies the method of claim 1 wherein multiple aliquots of each of IFN-g and the second IR-1 promoting agent are administered to the patients and wherein at least 48 hours elapse between aliquots. Claim 35 embodies the method of claim 1 wherein IFN-g and the second IR-1 promoting agent are separately administered not more than two hours apart. Claim 36 embodies the method of claim 1 wherein IFN-g and the second IR-1 promoting agent are separately administered more than two hours apart.

The combination of Yu and Nishimura et al and Cameron et al and Ferrero et al render obvious the specific embodiments of claims 1-3, 5, 10, 14, 16-20, 25, 28-30, 34, 37, 41, 44-49 and 81 for the reasons set forth above. Neither of the aforesaid references teach the intervals between the administration of the agents. However, the determination of determination of optimized conditions for administration of the second IR-1 promoting agent and the antigen-releasing agent or IFN-g is within the purview of one of skill in the art and is thus obvious over the combined references.

24. All other rejections and objections as set forth in the previous Office action are withdrawn.

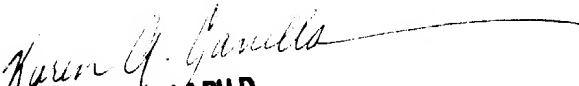
25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Karen A. Canella, Ph.D.

8/24/2004


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PRIMARY EXAMINER